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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,894	08/26/1999	MING LI	004.00191	7158

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Offic Action Summary	Application No.	Applicant(s)	
	09/383,894	LI, MING	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or

WILLIAM N. PHILLIPS
PATENT ANALYST

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the CRF Supplied by Applicant in response to the Notice to Comply (mailed 04-20-01) was never received by the Office. The CFR of the sequence listing as presently entered does not list all of the sequences in the instant case. It is requested that Applicant provide a new CRF of the sequence listing (as filed with their response to the Notice to Comply filed on 08-24-01) as well as a letter stating that the CRF and paper listing are the same. The Examiner apologizes for the inconvenience.

A complete response to this Office action must comply with this request.

Election/Restriction

Applicant's election without traverse of Group IX in Paper No. 8 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-49 are maintained as rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the prior Office action (mailed 09-12-00), because the specification, while being enabling for modifying beta cell insulin secretion using known calcium channel blockers, does not reasonably provide enablement for modifying beta cell insulin secretion using any calcium channel blocker or inhibitor of channel formation, ribozyme, antisense or an expressed gene *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection of record is set forth as follows.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 43-49 are drawn broadly to methods of modulating insulin secretion in pancreatic beta cells by modifying levels of functional T-type calcium channels by any mechanism, including modulating insulin secretion *in vivo* (whole organism). Claims 43-46 are further drawn to modifying levels of functional T-type calcium channels using antisense or expressing a nucleic acid encoding a T-type calcium channel in any setting, including *in vivo* (whole organism).

The specification provides examples wherein T-type calcium channel blockers, including mibefradil and $NiCl_2$ are administered to pancreatic cells, *in vitro* (cell culture) and T-type calcium channel activity is blocked. There are no examples provided in the instant specification wherein an inhibitor of channel formation, an antisense molecule, a ribozyme or an expressed pancreatic T-type calcium channel are demonstrated to alter insulin secretion in beta cells in any setting, including *in vitro*. Further, there are no examples provided by the instant specification wherein an antisense molecule or a ribozyme are demonstrated to alter the level of a T-type calcium channel or alter the expression of a nucleic acid encoding a T-type calcium channel in any setting, including *in vitro*.

At the time the instant invention was made, modifying insulin secretion in beta cells in vivo (whole organism) via calcium channel blockers was unpredictable (see for example Verma, S. et al. page 126), calcium channel blockers reported to inhibit insulin secretion *in vitro* do not predictably produce the same effect *in vivo*. The reason for this variability was unknown, and one skilled in the art would not be able to predict what calcium channel blockers would modify insulin secretion *in vivo* (whole organism), based on *in vitro* screening.

Further, the claimed methods read on *in vivo* (whole organism) methods of modifying insulin secretion using nucleic acid based drugs, including antisense, ribozymes and gene therapy methods. At the time the instant invention was made, and even now, *in vivo* (whole organism) methods using antisense, ribozymes and gene therapy were highly unpredictable (see, for example,

Branch, Agrawal, Rossi, Anderson and Verma, I. et al.) due to issues including the determination of accessible target regions, how to specifically deliver an antisense molecule, ribozyme or gene therapy vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene.

The specification, as filed, provides only general guidance with regard to such factors. Due to the unpredictability in the art, the field to date does not have guidelines which would enable one skilled in the art to routinely practice methods drawn to *in vivo* applications of antisense, ribozymes and gene therapy. As such, one skilled in the art would need to determine such factors de novo, through empirical, undue trial and error experimentation. The skilled artisan would need to first determine what compounds interfere with T-type calcium channel pore formation and what ribozyme and antisense sequences are able to inhibit the expression of a nucleic acid encoding a pancreatic T-type calcium channel, *in vivo* or *in vitro*. Further, one skilled in the art would need to determine which of these compounds change the level of functional t-type calcium channels in a manner and to the degree that insulin secretion would be modified. Additionally, one skilled in the art would need to determine how to deliver antisense molecules, ribozymes or gene therapy vectors specifically to pancreatic beta cells, in vivo, at a concentration which is effective to change the level of functional t-type calcium channels, and modify insulin secretion in said beta cells. This would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life

and stability of the antisense or ribozyme molecule *in vivo*. For gene therapy, in particular, it would require the determination of an appropriate vector and enhancer-promoter combination for beta-cells "the search for such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3) in order to get a high and sustained expression of a t-type calcium channel, such that beta cell insulin secretion would be modified.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor, the lack of working examples, and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Response to Arguments

Applicant's arguments filed 03-16-01 have been fully considered but they are not persuasive. In response to the rejection of record of claims 43-49 under 35 U.S.C. 112, first paragraph, as not being enabled over the full scope claimed, Applicant argues that the specification demonstrates that when the levels of T-type calcium channels in pancreatic beta cells is modified, insulin secretion by those pancreatic beta cells will be modified and that the particular method of modification is not relevant. Applicant argues that issues regarding the ability to administer antisense and other inhibitors and whether or not such inhibitors work in vivo is not relevant to the claimed methods. Applicant argues that they have discovered the concept that

when the levels of T-type calcium channels are modified in pancreatic beta cells that the level of insulin secretion by those cells is modified and, as such, they should not be required to limit the methods by which the levels of T-type calcium channels are modified.

These arguments have not been found persuasive because the claims clearly encompass methods wherein the level of T-type calcium channels is modified in vivo, including wherein the levels of T-type calcium channels are modified by inhibiting the expression of T-type calcium channels using antisense. These methods are encompassed by the claims and are clearly contemplated by the specification. The specification, however, does not enable methods of modifying the levels of T-type calcium channels over this scope, as detailed in the rejection of record set forth in the prior Office action (mailed 09-12-00) and repeated herein. To practice the methods claimed in vivo and by using nucleic acid based inhibitors (for example antisense, gene therapy, ribozymes) one skilled in the art would need guidance beyond the concept argued by Applicant, and would need to practice undue trial and error experimentation to actually practice the claimed methods over that scope. The specification has not provided guidance to the skilled artisan that would overcome the art recognized hurdles to the application of the claimed method in vivo and with the nucleic acid based inhibitors encompassed within the claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43 and 47 are maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Verma, S. et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth as follows.

Verma, S. et al. disclose a method wherein hypertensive rats are administered mibefradil, a T-type calcium channel blocker, with a resultant decrease in insulin secretion, which would necessarily be a decrease in insulin secretion by the rat beta cells.

Therefore, Verma et al. anticipates claims 43 and 47.

Claims 43 and 47 are maintained as rejected under 35 U.S.C. 102(a) as being anticipated by Bhattacharjee et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth as follows.

Bhattacharjee et al. disclose a method wherein rat beta cells (INS-1) are contacted *in vitro* (cell culture) with $NiCl_2$, with a dose dependent reduction in glucose stimulated insulin secretion.

Therefore, Bhattacharjee et al. anticipates claims 43 and 47.

Claim 43 is maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Kato et al. for the reasons of record set forth in the prior Office action (mailed 09-12-00). The rejection of record is set forth is set forth as follows.

Kato et al. disclose a method wherein neonatal rats are treated with streptozocin, increasing the level of functional T-type calcium channels, evidenced by the increased Ba^{2+} induced currents, and increasing insulin secretion.

Therefore Kato et al. anticipates claim 43.

Response to Arguments

Applicant's arguments filed 03-16-01 have been fully considered but they are not persuasive.

In response to the rejection of claims 43 and 47 under 35 U.S.C. 102(b) as being anticipated by Verma, S. et al. Applicant argues that Verma S. et al. teach away from the claimed invention because they state "it is reasonable to suggest that the effects of the drug [mibefradil] on insulin levels were independent of changes in pancreatic insulin release." Applicant argues that this teaching in Verma, S. et al. means that the claimed methods cannot be anticipated by this reference.

These arguments have not been found to be persuasive. The methods disclosed by Verma, S. et al. comprise all the method steps in the claimed method and utilize the same inhibitor as methods disclosed in the instant specification an encompassed in the claims and would, therefore,

anticipate the claimed method. Verma, S. et al. may suggest a different mechanism than the mechanism disclosed in the instant specification, however, given that the methods disclosed by Verma, S. et al. use the same inhibitor and comprise the same method steps as those in the instant specification it is presumed that the mechanism of action is the same. The mechanism disclosed by the specification does not distinguish the claimed methods from that disclosed by Verma et al.

In response to the rejection of claims 43 and 47 under 35 U.S.C. 102(a) as being anticipated by Bhattacharjee et al., Applicant argues that the reference Bhattacharjee et al. is not available as a prior art reference because it was published less than one year prior to the filing of the instant Application and that Applicant would submit a declaration stating that the Applicant (Ming Li) is the sole inventor of the material disclosed in Bhattacharjee et al., and not the other listed authors of said publication. These arguments have not been found to be persuasive because no declaration was filed.

In response to the rejection of claim 43 under 35 U.S.C. 102(b) as being anticipated by Kato et al. Applicant argues that Kato et al. teaches away from the claimed invention because Kato et al. state that the role of T-type calcium channels is unknown in the excitation-secretion coupling of beta cells and, therefore, do not anticipate the claimed methods. This argument has not been found to be persuasive because the methods disclosed by Kato et al. comprise the method steps of the claimed invention and utilize an inhibitor specifically disclosed by the instant

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523. The Examiner can normally be reached Monday-Thursday from 8:30 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
November 13, 2001

SEAN McGARRY
PRIMARY EXAMINER

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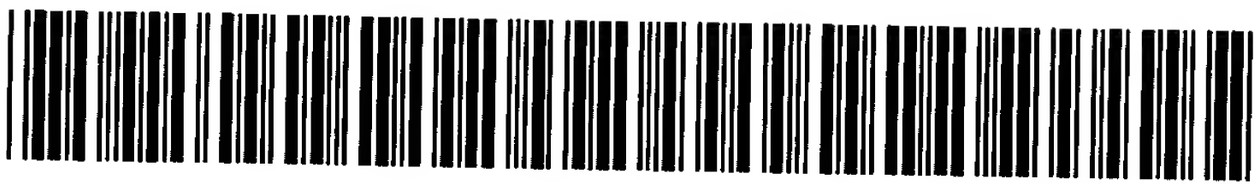

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